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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/910,186	07/20/2001	Leonard A. Smith	A33626A 067252.0107	8442

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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/910,186	Smith et al	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *42-51,53,55,56,82,85 and 86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *42-51,53,55-56,82,85-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 42-51,53,55-56,82, 85-86 are pending.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

1. This application is claiming the benefit of a prior filed nonprovisional application under 35 U.S.C. 120, 121, or 365(c). Copendency between the current application and the prior application is required. Application serial number 08/123,975, filed September 1993 was abandoned on June 20, 2001 and the instant specification was afforded the filing date of July 20, 2001; co-pendency between 08/123, 975 and the instant Application 09/910,186 did not exist, therefore the instant Specification can not claim priority to 08/123,975.

Specification

2. This is a reiteration of the Improper Incorporation by Reference made of record in the Office Action dated May 29, 2003.

3. The attempt to incorporate subject matter into this application by reference to Whelan et al (1992, Applied and Environmental Microbiology) and Thompson et al (1990, European Journal of Biochemistry) is improper because the incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, **stating that the amendatory material consists of the same material incorporated by reference in the referencing application**. See *In re*

Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

4. The essential material Applicant seeks to incorporate by reference is directed to disclosed nucleic and amino acid sequences of Whalen et al and Thompson et al.

5. A general statement at page 44, lines 18-20, of the instant Specification, incorporating information contained in published journal articles or foreign documents by **reference is not sufficient** *to claim essential information contained or disclosed* in the Thompson et al and Whelan et al references.

6. An effective, executed Affidavit or Declaration has not been submitted. At page 15, of the instant Amendment submitted by Applicant December 3, 2003 declaring that SEQ ID NO 40 and SEQ ID NO 41 are portions of the sequence disclosed by the two references does NOT comply with the MPEP section 608,01(p), page 600-80, subparagraph 2 which requires an affidavit or declaration executed by the applicant or a practitioner representing the applicant, which states the amendatory material consists of the "same material incorporated by reference in the referencing application".

Continued Examination Under 37 CFR 1.114

7. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 3, 2003 has been entered.

Rejections Withdrawn

8. Claims 42-43, 45-47, 55-56 rejected under 35 USC 101 has been obviated through amendment of claim 42 to recite a combination of claim limitations to show the "hand of man", specifically "isolated or purified".

9. Claims 42-51, 53, 55-56, 82 and 85-86 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement in light of the claims having been amended to no longer recite the phrase "A nucleic acid comprising a nucleotide sequence".

10. Claim 53 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reciting an incomplete method of producing an immunogenic composition has been obviated in so far as the claim has been amended to be directed to a method of isolating a polypeptide.

11. Claim 42 objected to because it depended from a later claim 43 has been obviated through amendment of claim 42.

12. The submitted terminal disclaimer upon being found effective obviates the Obviousness Type Double patenting made of record in the Office Action dated May 29, 2003.

13. Claim 43, rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reciting the phrase "said amino acid sequence comprising at least one immunogenic epitope" has been obviated based upon the fact that Applicant stated at page 16, of the Amendment paragraph 4, that the recited immunogenic epitope is inherent in SEQ ID NO 8,

and therefore does not read on the presence of a heterologous epitope, as in a fusion protein, an embodiment exemplified in the instant specification.

Rejections/Objections Maintained

14. The amendment filed March 7, 2003 remains objected to under 35 USC 132, because it introduces new matter into the disclosure.

Response to Arguments

15. Applicant's arguments filed December 3, 2003 have been fully considered but they are not persuasive.

16. The amendment filed March 7, 2003 objected to under 35 USC 132, because it introduces new matter into the disclosure is traversed on the grounds that the instant Specification claims priority to 08/123, 975 and the disclosure of Thompson et al and Whelan et al were both incorporated by reference, concluding that no New Matter has been added to the Specification.

17. The examiner upon reconsideration of the earliest priority claimed, SEQ ID Nos 37, 39, 40 and 41 recite NEW Matter as the earliest priority claimed from Application serial number 08/123,975 has not and can not be perfected as the earliest application was abandoned at the time of filing of the Specification of the instant Application, and the material incorporated by reference to two published journal articles was not accompanied by an effective executed Affidavit or Declaration. The specification remains objected to under 35 USC 132, as the Amendments of the specification introduce New Matter at least at page 12, lines 7-14; page 13, lines 1-6; page 38, lines 6-7.

Claim Amendments/New combination of Claim Limitations/New Grounds of Rejection

Specification

18. The disclosure is objected to because at page 14, lines 12-28, Table 1 is referred to but the specification does not show or provide information contained in a Table 1; NO New Matter should be submitted in response to this objection, but where the information referred to, and contained in Table 1 is located in the instant specification should be pointed out so the narrative with respect to Table 1 can be clearly understood . Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

19. Claims 46 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reciting the phrases "wherein said expression control sequence comprises a promoter" and "wherein said expression control sequence comprises an enhancer", respectively and depend from claim 42 which recites the limitations "An isolated and purified nucleic acid". The phrases recited in claims 46 and 47 lack antecedent basis in claim 42. There is insufficient antecedent basis for these limitations in claim 42. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed. While the nucleic acid of claim 42 may or may not comprise an expression control sequence, the structural sequence was and is not positively recited in claim 42. Amendment of claims 46 and 47 should depend from claim 45.

20. Amended Claim 48 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reciting the step of "culturing the transfected cell under conditions wherein the nucleic acid is expressed". The method is incomplete. Expression of a nucleic acid defines the step of transcription which is nucleic acid expression, not translation into a polypeptide. The method is directed to a method of preparing a polypeptide, the method is not a Jepsen claim that defines a new methods step in a method of preparing a polypeptide, but should positively recite the step of preparing the polypeptide, or the step of – "under conditions in which the nucleic acid is expressed - - - and the polypeptide produced and prepared- - - . The instantly claimed invention, based upon the methods steps recited, is a method of culturing a transfected cell that encodes a polypeptide, not a method of preparing a polypeptide, therefore the method recited in the preamble of the claim is not clearly set forth and distinctly claimed.

21. Claims 49 and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reciting the phrase "at least one insoluble polypeptide". What makes the polypeptide insoluble? While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed. The structure required to make the polypeptide insoluble is not positively recited in the claim. Additionally the source of the immunogenic epitope is not recited in the claim to be SEQ ID NO 8; the claim should clearly define the source or type of

immunogenic epitope. Is the epitope a heavy chain botulinum neurotoxin serotype B epitope? The specification at page 89, line 6 defines the polypeptide to be in an "insoluble protein fraction", and not to be an insoluble polypeptide. What the structure of the insoluble polypeptide is, is not distinctly claimed, nor is it clearly defined. The instant specification defines the expressed Hc protein to be fractionated in order to obtain an insoluble protein fraction. The invention is not clearly and distinctly claimed.

22. Claims 50 and 51 recite the limitation "said organism " but the term "cell" is recited in claim 48 from which they depend. There is insufficient antecedent basis for the term "organism" in the claim. Claims 50-51 should recite the term –cell--.

23. Claim 53 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention; the claim has been amended to recite the phrase "the recovered polypeptide". The term "recovered" lacks antecedent basis in the claim which has been amended to recite the step of "isolating". Amendment of the claim to recite - - - the isolated polypeptide- - - could obviate this rejection.

24. Claims 42-47, 48-51, 53, 55-56, 82, 85-86 have been amended to recite the phrase "encoding a polypeptide having the amino acid sequence of SEQ ID NO 8, said amino acid sequence comprising at least one immunogenic epitope." The specification has defined the invention to include or comprise peptide fragments that encode protective epitopes (see the instant specification at page 16, line 8 "immunogenic peptide fragments"; page 15, lines 13-15; page 15, lines 7-12; page 24, lines 11-15) as well as an entire synthetic Hc protein for serotype B botulinum neurotoxin. The recitation of SEQ ID NO 8 to define the polypeptide and then to be

directed to polypeptide fragments that comprise "at least one immunogenic epitope" is confusing. The claims are not internally consistent through defining the invention to be the polypeptide with the amino acid of SEQ ID NO 8, and later redefines the claimed invention to be polypeptides that have a single immunogenic epitope. This combination of claim limitations recited is confusing in light of the fact that SEQ ID NO 8 is the amino acid sequence for the entire synthetic protein Hc carboxy-terminal of the botulinum neurotoxin serotype B, and comprises a plurality of epitopes. The claims through the recitation of the phrase "at least one immunogenic epitope" changes the invention to be directed to fragments of SEQ ID NO 8. The invention is not distinctly claimed in light of SEQ ID NO 8 comprises more than just one epitope, and to define the invention to only comprise a single epitope is inconsistent with the fact that SEQ ID NO 8 has an amino acid sequence of more than 400 amino acids and comprises a plurality of epitopes not just a single epitope. All of the claims appear to be claiming the entire coding sequence for SEQ ID NO 8, but the coding sequence encodes more than one epitope, and therefore defines the claimed invention to be directed to a plurality of nucleic acids that comprise any nucleic acid that encodes an immunogenic epitope with an amino acid sequence of SEQ ID NO 8. The claims do not set forth a species of nucleic acid that only comprises a single epitope through the recitation of SEQ ID NO 8. The combination of claim limitations do not clearly set for the invention.

25. Claims 85-86 recite the "wherein said polypeptide is at least 0.75% (w/w) of the total cellular protein", and "wherein said polypeptide is at least 20 % (w/w) of the total cellular protein", respectively and depend directly or indirectly from claims 42, 45 and 82. The nucleic acid of claim 45 comprises an expression control sequence, but the sequence has not been so

claimed to define it to be a constitutive control sequence, nor has it been defined to be an inducible control sequence, or a ribosomal binding control sequence. How is the polypeptide of claims 85-86 present in the claimed host cell of the recited percentage cellular protein if the polypeptide is not expressed ? The phrase "total cellular protein" lacks antecedent basis in all of the claims from which claims 85-86 depend. Clarification is requested.

Claim Rejections - 35 USC § 102

26. Claims 42-47, 55-56, 82-86 are rejected under 35 U.S.C. 102(b) as being anticipated by Halpern et al (May 1993, reference of record) .

Halpern et al (May 1993) disclose the claimed invention directed to a nucleic acid that comprises a nucleic acid sequence of the carboxyl terminal portion of a botulinum neurotoxin, wherein the nucleic acid encodes an amino acid sequence conserved across Clostridial neurotoxins to include botulinum toxin B. The disclosed nucleic acid comprises a nucleic acid sequence of SEQ ID No 7 and encodes the amino acids CCDEGWT" of SEQ ID NO 8 (see page 1 1189, col. 1, preparation of antibodies lines 1-2; Figure 1, and results section, that defines the nucleic acids (DNA) were capable of being expressed as they had a -1-7 RNA polymerase promoter and start codon added at the 5' end of the nucleic acids (see col. 2, page 11189, first paragraph; see page 11186, col. 2, experimental procedures, paragraphs 2-3).
The isolated nucleic acid encoded a synthetic polypeptide (see page 1 190, col. 1, second paragraph) that was formulated into an immunogenic composition (see page 11189, col. 1, paragraph 5).The heavy chain nucleic acid molecules that comprised the carboxyl terminal encoded polypeptides were cloned . The recombinant mammalian host cells were cultured (see page 2255, col. 2, paragraph 2), the expressed (transcribed and translated) protein was then

recovered for amino acid sequencing (see page 2258, Figure 8 and page 2258, col. 2, paragraph 1; table 3, top of page 2260; purified polypeptide, see page 11190, col. 1 first paragraph; see page 2255, col. 2, paragraph 5). The reference anticipates the instantly claimed invention.

27. Claims 48 and 51 are rejected under 35 U.S.C. 102(a) as being anticipated by Smith et al. (different inventive entity, priority date for yeast: Pichia pastoris claims, is not 1993, reference of record).

Smith discloses the claimed invention of a nucleic acid that encodes a Clostridium botulinum type B- Hc capable of being expressed in a yeast, specifically Pichia pastoris. Smith discloses a recombinant Pichia pastoris host cell that encodes of type B Clostridium botulinum neurotoxin (see Figure 6, legend narrative page 1546). A method of producing an immunogenic polypeptide is disclosed, the method comprising the steps of culturing the recombinant Pichia pastoris host cell and recovering the expressed Hc polypeptide was purified through cell extraction. An immunogenic composition was formulated and used in vaccine challenge experiments in mice (see page 1547 top of page). Smith anticipates the claimed invention.

28. Claims 42-47, 48-49, 50, 55, 82 are rejected under 35 U.S.C. 102(b) as being anticipated by Whelan, SM et al (Accession Number M81186, reference of record) for reason of record in light of all of the claims reciting the phrase "said amino acid sequence comprising at least one epitope, thus claiming an isolated or purified nucleic acid that encodes an immunogenic epitope of the Hc domain of serotype B botulinum neurotoxin (see Whalen et al, entire reference, especially Figure 3, pages 2350-2351; page 2352, consensus sequence col. 2) showing conserved

sequences that include at least one epitope across species of botulinum neurotoxin to include botulinum serotype B neurotoxin.

29. The percentage AT in the nucleic acid is "less than about 70%" which encompasses amounts above and below 70% through the recitation of the term "about", which would include values of 74.5% (less than 10% variance from 70%, less than 77%) (see page 2346, column 2, paragraph 1 (74.6%).

Whelan et al disclose the claimed invention directed to a nucleic acid comprising a nucleic acid which encodes the carboxyl-terminal portion of the heavy chain of botulinum neurotoxin serotype B, specifically 99.773 % of SEQ ID NO 8. The nucleic acid was cloned and expressed and found to encode a polypeptide of 623 amino acids of the H chain (see abstract), which includes a portion of the carboxyl terminal of the heavy chain of botulinum toxin B. The nucleic acid of Whelan et al would be capable of being recombinantly expressed in an organism selected from the group consisting of gram negative bacteria, yeast and a mammalian cell line.

Whelan et al anticipate the instantly claimed invention as now claimed.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on 7:30-5:00 M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp

March 16, 2004

MARK NAVARRO
PRIMARY EXAMINER